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(54) Title: COLD/SINUS PREPARATION CONSISTING OF PHENINDAMINE TARTARATE WITH OR WITHOUT THERAPEUTIC AGENTS

(57) Abstract

The present invention is an improved pharmaceutical composition useful in the treatment of colds, sinus and allergies comprising an unstable antihistamine such as phenindamine that is stabilized in a non-aqueous, inert carrier system. More specifically, the phenindamine is stabilized in a mineral oil/fumed silica particle matrix which so stabilizes the compound that additional, otherwise reactive drugs such as analgesics, decongestants and expectorants can be incorporated for a more effective, multi-system formula.

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Cold/Sinus Preparations Consisting of Phenindamine Tartarate With or Without Therapeutic Agents

Background of the Invention

The present invention is an improved pharmaceutical composition for use in the treatment of sinus, allergy and cold symptoms consisting an otherwise unstable antihistamine that is stabilized through its incorporation in a non-aqueous inert carrier system. More specifically, the present invention relates to the use of the antihistamine phenindamine in the treatment of colds, sinus and allergies in a composition that is stabilized, notwithstanding the presence of moisture and/or other reactive ingredients. This allows for the creation of a sinus-cold remedy comprising phenindamine and other analgesic and decongestant actives.

Phenindamine (2,3,4,9-tetrahydro-2-methyl-9-phenyl-1H-indeno [2,1-c] pyridine) is a stable, white crystalline powder that was first described in 1949 in U.S. Patent No. 2,470,108. The tartrate salt is soluble up to 3% in water, and is sparingly soluble in propylene glycol. Unlike other antihistamines in common use, phenindamine does not produce drowsiness and on the contrary, has a mild stimulating effect on some patients and may even cause insomnia in some if taken before bedtime. This is clearly an advantage for cold and allergy sufferers over the currently available products which make many feel sleepy or drowsy when taken during the day.

The use of phenindamine however, has been curtailed because of its inadequate antihistamine properties that are a direct result of its chemical instability. This may be due to its tendency to isomerize to an inactive form, isophenindamine. The isomerization reaction has been found to occur when phenindamine is stored in both wet and dry states and the reaction is enhanced in solutions having an alkaline pH or when the antihistamine is formulated with oxidizing substances.

A need exists for a nonsedating, and yet mild, antihistamine product which is storage stable for long periods of time when phenindamine is used in the presence of alkaline buffers and known oxidizing agents. Numerous attempts have been made in the prior art to entrap pharmaceutically active ingredients to enable the formation of sustained release formulations that dissolve or erode in the gastrointestinal tract.

United States Patent No. 5,025,019 to Sunshine et. al. discloses pharmaceutical compositions comprised of a non-steroidal anti-inflammatory drug such as ibuprofen in combination with a sympathomimetic amine such as pseudoephedrine and an antihistamine, one of which is phenindamine. The tri-partate active is combined with any one or mixture of a variety of pharmaceutically inert carriers such as lactose, cellulose, starch, polyethylene glycol and the like but there is no evidence or suggestion of enhanced stability.

United States Patents Nos. 4,364,945 and

4,269,835 to Whittle disclose a nasal composition for relieving sinus distress comprised of an antihistamine and tocopherol (Vitamin E) or one of its isomers. The nasal spray does not include a nasoconstrictor which is allegedly found in most other sprays and actually counteracts the sympathomimetic relief of the antihistamine. Phenindamine tartarate is listed as one of a number of suitable antihistamines useful in the practice of the invention. No regard is given to its stability characteristics however, nor any solution to the problem suggested.

A series of United States Patents 4,840,962; 4,749,723; 4,749,720; 4,749,697 and 4,619,934 also to Sunshine et. al. disclose cold/cough mixtures comprising a combination of an antihistamine and a non-steroidal anti-inflamatory compound (NSAID). Phenindamine is listed as one of many suitable antihistamines in each patent and each one discloses a combination of antihistamine with a different class of NSAID. There is no mention or teaching of the drug's stability problems or their solutions nor are any suggestions of the use of mineral oils and silica gel carrier matrices suggested as a means towards this goal.

United States Patent No. 4,820,523 to Shtohryn et.al. also discloses a pharmaceutical composition for the treatment of colds, allergies and sinus problems, which comprises an effective amount of a pharmaceutically acceptable salt of phenindamine entrapped in a leachable non-toxic wax matrix in combination with at least one analgesic, decongestant, antitussive and mixtures

thereof. The formulation allegedly provides for the immediate release of phenindamine so that within one hour, over 70% of the drug is dissolved out of the wax matrix. Also, it is asserted that the wax matrix prevents any isomerization of the active compound even in the presence of moisture, alkali and the like.

U.S. Patent No. 2,875,130 discloses a method of preparing a sustained release pharmaceutical powder which comprises reducing a solid medicament to a particle size of a maximum of about 10 microns, mixing the thus formed particles in a liquefied lipid material from about 5% to about 35% by weight of the total formulation which is substantially water insoluble and has a melting point of about 85° C., solidifying the thus formed mixture and then grinding it to form a primary powder having a maximum particle size in the range of from about 5 to 25 microns. The powder is then mixed again with a melt of a lipid material of from about 25% to about 85% by weight which is substantially water insoluble and has a melting point which is at least about 5°C. lower than the melting point of the first mentioned lipid material. The temperature of the melt is maintained below the melting point of the first mentioned lipid material and above the melting point of the second mentioned lipid material and the powder-lipid mixture is mixed with water to form an emulsion. The emulsion is then cooled to a temperature below the melting point of the second mentioned lipid material to precipitate the sustained release pharmaceutical powder, said

solid powder having a melting point higher than the second mentioned lipid material. These methods of drug entrapment and coating are both time consuming and expensive due to the materials used and processing parameters required to work with them. Secondly, when large amounts of wax or lipid materials are used, the pathways for drug release are often curtailed or affected so as to not result in proper, uniform release.

It is an object of the present invention to provide an improved pharmaceutical composition useful in the treatment of colds, sinus and allergy that is stable over time until consumption even in the presence of moisture and other chemical compounds which otherwise detract from the drugs effectiveness. More specifically, it is an improved pharmaceutical composition comprising phenindamine which is stabilized in a non-aqueous, inert carrier system that allows for the additional incorporation of other analgesics and decongestants which would otherwise adversely affect the drugs stability and potency.

Summary Of The Invention

The present invention is an improved pharmaceutical composition useful in the treatment of colds, sinus and allergies comprising an unstable antihistamine such as phenindamine that is stabilized in a non-aqueous, inert carrier system. More specifically, the phenindamine is stabilized in a mineral oil/fumed silica particle matrix which so stabilizes the compound that additional, otherwise reactive drugs such as

analgesics and other decongestants can be incorporated for a more effective, multi-system formula.

Detailed Description Of The Present Invention

The present invention comprises the stabilization of an otherwise unstable antihistamine such as phenindamine by incorporating it in a non-aqueous, inert carrier system. Antihistamines like phenindamine possess poor chemical stability as they are readily converted into their inactive isomers such as isophenindamine when subjected to moisture, alkali, polyvalent metal salts and various therapeutic agents. Hence, although phenindamine is recognized as a highly effective antihistamine and is of even greater value due to its mild stimulating effect, its use in a multi-symptom formula has not been optimally achieved since many of the analgesics and other decongestants with which it could be combined result in the detrimental isomerization reaction.

The surprising and unexpected stability of phenindamine that is achieved even in the presence of other reactive elements results from mixing it in a non-aqueous, inert matrix, preferably comprised of a liquid petroleum derivative such as mineral oil in combination with a fumed silica matrix. Without being bound to any particular theory, it is believed that during the process of preparation, the phenindamine particle acts as a core onto whose surface smaller mineral oil beads or droplets become adsorbed. The

drug/oil agglomeration is then absorbed into the larger, fumed silica particles. A decongestant such as pseudoephedrine, is mixed into the matrix and is also absorbed into the silica particle but subsequently leaches out of the particle as sintered crystals and the entire composition is again further coated with a uniform layer of mineral oil. Preferably, the pharmaceutical composition is then packaged and administered in gelatin capsules.

As pointed out previously, the benefit of the above described pharmaceutical composition is that it can be combined with additional analgesics, decongestants and expectorants to prepare an effective multi-symptom formula. The unstable phenindamine is protected from reacting with the other actives which would otherwise result in its isomerization and inactivity. Non-limiting examples of useful analgesics include acetaminophen, aspirin, salicylamide, phenacetin, ibuprofen, choline salicylate, magnesium salicylate, salicylate salts, salsalate, sodium salicylate, trolamine salicylate, diclofenac, diflunisal, fenoprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, sulindac, tolmetin and mixtures therein.

Suitable decongestants may be selected from the group consisting of, phenylephrine hydrochloride, phenylpropanolamine, pseudoephedrine hydrochloride, ephedrine sulfate and mixtures there f, while suitable antitussive materials may be selected from the group

comprising dextromethorphan, dextromethorphan hydrobromide, codeine, noscapine, hydrocodone, carbetapentane citrate, benzonatate, clophedianol hydrochloride and mixtures thereof.

Suitable expectorants that may be used in combination with phenindamine and/or the other actives in the practice of the present invention include guaifenesin, iodinated glycerol, potassium iodide and mixtures thereof, to name a few.

The phenindamine is formulated as its pharmaceutically acceptable salt. Such salts may be selected from a wide range of materials and includes salts from the group consisting of citrate, hydrobromide, hydrochloride, maleate, succinate, sulfate, tartrate, and mixtures thereof. Phenindamine tartrate is the preferred active form of the drug. The amount of phenindamine used in the total formulation will depend on the dosage necessary to achieve the desired therapeutic effect. This amount may be provided by employing from about 0.5 to 99% by weight phenindamine in the mineral oil/fumed silica gel matrix. Generally, the amount of phenindanime incorporated in conventional formulations will range from 25 mgs to 100 mgs per capsule for adults, and from about 12.5 to 15.0 mgs. per capsule for children.

The amounts of the other active ingredients when employed vary according to the dosage regimen and will depend upon the type and number of drug(s) used in combination with phenindamine. Exact ratios can readily be determined by one skilled in the art and can be tailored according

to the therapy schedule. For example, the ratio of acetaminophen:phenindamine must be much greater than the ratio of, for example destromethorphan: phenindamine in order for a therapeutic analgesic effect. FDA monographs and NDA's can be reviewed for this purpose.

The mineral oil can be incorporated in amounts of from about 1.0%, to 99% of the total weight of the matrix and preferably from about 15% to about 90%. The fumed silica particles can comprise of from about 10% to about 99% of the total weight of the matrix and preferably from about 5% to 90%.

The following examples are provided to better teach the pharmaceutical compositions of the present invention and methods for their preparation. They are for illustrative purposes only however, and it is realized that minor changes can be made with regard to the materials and process parameters which would not materially alter or affect the end product or result. The examples should therefore not be deemed as limiting the spirit and scope of the present invention as recited in the claims that follow.

Example I

Ten (10) gm. of phenindamine tartarate were placed in a 600 ml. beaker and mixed with 200.00 gm. mineral oil (Kaydol®) for five minutes. This was then homogenized. 10.0 gm. of fumed silica gel (Cabosil) was then added until a thick, off-white uniform paste was achieved. A second equivalent amount of mineral oil was additionally

added and blended until a second, less viscous lotion-like suspension was formed. The composition was then filled in soft gelatin capsules.

Example II

Ten (10) gm. phenindamine tartarate was mixed with 290.00 gm. of mineral oil at high shear for 10 min. until a homogeneous, viscous dispersion was produced. To this as added 8.0 gm. Cabosil® fumed silica particles and this was mixed for an additional 7.0 min. At this point, 24.00 gm. pseudoephedrine Hcl was added while mixing was continued for five more minutes. A second allotment of mineral oil 40.0 gm was added and the blend mixed another 5 min. The off-white, viscous composition was again dispensed into individual soft gelatin capsules.

Examples III

The following formulations were provided

Formulation	A	B
Polyethylene glycol (PEG)	90.0 gm	101.6 gm
Phenindamine tartarate	10.0 gm	10.0 gm
Cabosil Silica Gel	5.0 gm	8.0 gm
Pseudoephedrine Hcl		24.00 gm
		143.6 gm

The polyethylene glycol and phenindamine tartarate were mixed at high shear for 3 min. until the powder was well dispersed. In formulation B, the pseudoephedrine Hcl was also

added for its decogestant properties. Cabosil silica particles were then added and mixed until the mixture was uniform. It was then put into soft gelatin capsules and set aside.

Example IV

Ten (10) gm. of phenindamine tartarate were mixed as before in about 117.0 gm of polyethylene glycol 400 until thoroughly dispersed. To this was added 24 gm. pseudoephedrine Hcl and 135.44 gm. acetaminophen. The mixture was blended for 5 min. at high shear when an additional 100.00 gm. polyethylene glycol was added. The off-white paste was put into soft gelatin capsules, each capsule thereby containing 325 mg. acetaminophen, 34 mg. phenindamine, and 57.6 mg. pseudoephedrine per dose.

Example V

The following formulations were prepared, following the same procedure as set forth in Examples I-IV

	Formulation C	Control
PEG 400	160.0 gm.	
Phenindamine tartrate	6.25 gm.	6.25 gm.
Pseudoephedrine Hcl	30.0 gm.	15.0 gm.
Acetaminophen	125.0 gm.	130.0 gm.
Mineral Oil	135.0 gm.	
Cabosil® Silica gel	3.00 gm.	

All three formulations were, as before, an off-white viscous paste which was subsequently encapsulated as dosage forms in soft gelatin

capsules. The capsules of Examples, I-II, III a+b, IV and V were bottled and allowed to stand for several weeks at accelerated temprature protocols (~40°C) so as to simulate worst case scenario warehouse conditions. The control began to discolor within one week, becoming gradually darker in color. The formulations of Examples III and IV as well as formulation C of Example V retained their off-white color somewhat longer, but not to the extent as the formulations of the present invention. (Examples I and II)

The experimental examples of the present invention retained their off-white appearance throughout, the mineral oil formulations exhibiting the least degree of color change and hence greatest stability over long periods of time. The discoloration of the control is indicative of drug degradation and inactivation while the retention of the off-white color by the formulations of the present invention indicates that no such degradation or reaction of the phenindamine with the other ingredients took place and therefore the drug remained stabilized and active.

Claims

What We Claim Is:

1. An improved pharmaceutical composition for use in the treatment of sinus, allergy and cold symptoms comprising an effective amount of a chemically sensitive antihistamine that is stabilized by a non-aqueous inert carrier system.

2. The improved pharmaceutical composition of claim 1 wherein said antihistamine is phenindamine tartarate.

3. The improved pharmaceutical composition of claim 2 wherein said non-aqueous, inert carrier system is a matrix comprised of mineral oil and fumed silica particles.

4. The improved pharmaceutical composition of claim 3 wherein said fumed silica also comprises silicon dioxide.

5. The pharmaceutical composition of claim 4 further comprising an analgesic agent.

6. The pharmaceutical composition of claim 5 further comprising a decongestant.

7. The improved pharmaceutical composition of claim 6 wherein said mineral oil comprises from about 1.0% to about 99% by weight of said matrix.

8. The pharmaceutical composition of claim 7 wherein said mineral oil comprises from about 15% to about 90% of the total weight of the matrix.

9. The pharmaceutical composition of claim 8 wherein said fumed silica particles comprise from about 5.0% to about 90% of the total weight of the matrix.

10. The pharmaceutical composition of claim 9 wherein said analgesic is selected from the group consisting of acetaminophen, ibuprofen, salicylate, magnesium salicylate, salicylate salts, salsalate, sodium salicylate, trolamine salioylate, diclofenac, diflunisal, fenoprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, sulindac, tolmetin, naproxen, asprin, piroxicam and mixtures thereof.

11. The pharmaceutical composition of claim 10 wherein said decongestant is selected from the group consisting of pseudoephedrine hydrochloride phenylpropanolamine, ephedrine sulfate and mixtures thereof.

12. The pharmaceutical composition of claims 1 or 2 wherein said antihistamine comprises from about 1.0% to about 85% by weight of the pharmaceutical composition.

13. The pharmaceutical composition of claim

12 further comprising an antitussive.

14. The pharmaceutical composition of claim 13 wherein said antitussive is selected from the group consisting of dextromethorphan, dextromethorphan hydrobromide, codeine, noscapine, carbetapentane citrate, hydrocodone, benzonatate, chlophedianal hydrochloride and mixtures thereof.

15. The pharmaceutical composition of claim 14 wherein said antitussive comprises from about 1.0% to about 50% by weight of the pharmaceutical composition.

16. The pharmacentical composition of claim 15 further comprosing an expectorant.

17. The pharmacentical composition of claim 16 wherein said expectorant is selected from the group consisting of quaifenesin, iodinated glycerol, potassium iodide and mixtures thereof.

18. A method for the preparation of an improved pharmaceutical composition useful in the treatment of colds, sinus and allergies comprising the steps of

a) mixing a chemically sensitive antihistamine in mineral oil to form a non-aqueous dispersion;

b) absorbing said dispersion into fumed silica particles.

c) applying additional mineral oil about the silica/antihistamine core and;

d) depositing said mineral oil coated cores in a soft gelatin capsule.

19. The method of claim 18 wherein said antihistamine is phenindamine tartarate.

20. The method of claim 19 further comprising the incorporation of an analgesic agent.

21. The method of claim 19 further comprising the incorporation of a decongestant.

22. The pharmaceutical composition of claim 21 wherein said mineral oil comprises from about 15% to about 90% of the total weight of the matrix.

23. The pharmaceutical composition of claim 22 wherein said fumed silica particles comprise from about 5.0% to about 90% of the total weight of the matrix.

24. The method of claim 23 wherein said analgesic agent is selected from the group consisting of acetaminophen, aspirin, ibuprofen, naproxen, piroxicam, salicylate, magnesium salicylate, salicylate salt, salsalate, sodium salicylate, trolamine salicylate, diclofenac, diflunisal, fenoprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, sulindac, tolmetin, and mixtures there f.

25. The method of claim 24 wherein said decongestant is selected from the group consisting pseudoephedrine hydrochloride, phenylephrine hydrochloride, phenylpropanolamine, ephedrine sulfate and mixtures thereof.

26. The method of claim 25 further comprising the incorporation of an antitussive.

27. The method of claim 26 wherein said antitussive is selected from the group consisting of dextromethorphan, dextramethorphan hydrobromide, codeine, noscopine, carbetapentane citrate, hydrocodone, benzonatate, chlophedianal hydrochloride and mixtures thereof.

28. The method of claim 27 further comprising an expectorant.

29. The method of claim 28 wherein said expectorant is selected from the group consisting of guaifenesin, iodinated glycol, potassium iodide and mixtures thereof.

30. A method for the treatment of colds, sinus or allergies in a mammal comprising the oral administration of the pharmaceutical composition of claims 1,2 or 8.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 94/00378

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/44 A61K9/14 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,H,000 672 (T.H.BAXTER) 5 September 1989 see claims 1-4,8,12,19,23,24 ---	1-30
Y	EP,A,0 241 615 (WARNER-LAMBERT) 21 October 1987 cited in the application see claims ---	1-30
Y	EP,A,0 219 458 (WARNER-LAMBERT) 22 April 1987 see claims see page 6, line 2 ---	1-30
A	WO,A,85 04589 (A.SUNSHINE) 24 October 1985 cited in the application see claims see page 21, line 1 - line 23 --- -/--	1-30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 May 1994	18. 05. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Scarponi, U

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Inte. ional Application No
PCT/US 94/00378

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,2 875 130 (G.M.GRASS) 24 February 1959 cited in the application see the whole document	1-30

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/00378

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 30 is directed to a method of treatment of the human body by therapy (Rule 39.1(iv) PCT) the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/US 94/00378

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-H-000672	05-09-89	NONE		
EP-A-0241615	21-10-87	US-A-	4820523	11-04-89
		AU-B-	569431	28-01-88
		AU-A-	6113786	22-10-87
		CA-A-	1267605	10-04-90
		DE-A-	3681582	24-10-91
		JP-B-	6021067	23-03-94
		JP-A-	62242619	23-10-87
EP-A-0219458	22-04-87	US-A-	4753800	28-06-88
		AU-B-	565750	24-09-87
		AU-A-	6345686	09-04-87
		CA-A-	1276885	27-11-90
		JP-C-	1595946	27-12-90
		JP-B-	2020604	10-05-90
		JP-A-	62116507	28-05-87
WO-A-8504589	24-10-85	US-A-	4552899	12-11-85
		AU-B-	589554	19-10-89
		AU-A-	4120085	01-11-85
		CA-A-	1258430	15-08-89
		DE-A-	3585495	09-04-92
		EP-A,B	0180597	14-05-86
		JP-T-	61501913	04-09-86
		US-A-	4749697	07-06-88
		US-A-	4839354	13-06-89
		US-A-	4749722	07-06-88
		US-A-	4749711	07-06-88
		US-A-	4749723	07-06-88
		US-A-	4749720	07-06-88
		US-A-	4749721	07-06-88
		US-A-	4783465	08-11-88
		US-A-	4920149	24-04-90
		US-A-	4840962	20-06-89
		US-A-	4871733	03-10-89
		US-A-	5025019	18-06-91
		US-A-	4619934	28-10-86
		US-A-	4738966	19-04-88

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/US 94/00378

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-2875130		NONE	